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On January 5, 2007
TOWNSEND and TOWNSEND and CREW LLP
Joe W. Gray

PATENT
Attorney Docket No.: 02307O-067720US
Client Ref. No.: 96-215-3



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

LALEH SHAYESTEH et al.

Application No.: 08/905,508

Filed: August 4, 1997

For: GENETIC ALTERATIONS
ASSOCIATED WITH CANCER

Customer No.: 20350

Confirmation No. 5513

Examiner: Jehanne Souaya Sitton

Technology Center/Art Unit: 1634

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Joe W. Gray, am a Professor of Laboratory Medicine and Radiation Oncology at the University of California San Francisco. I am a co-inventor of the subject matter disclosed and claimed in the above-referenced patent application.

2. I received a Ph.D. in Physics in 1972 from Kansas State University. My field of expertise is cancer and cytogenetics. I have been in this field for over 30 years and have authored over 300 publications in this area.

3. I have read and am familiar with the contents of the above-referenced patent application and claimed subject matter. I understand that the Examiner has rejected the current claims as allegedly unpatentable over the combination of the prior art teachings of Bonjouklian, *et al.* (U.S. Patent No. 5,378,725, "Bonjouklian") in view of Arnold, *et al.* (*Genes, Chromosomes, and Cancer* 16:46-54, 1996, "Arnold") and Volinia, *et al.* (*Genomics* 24:472-477,

1994, "Volinia") and further in view of Xiao, *et al.* (*International Journal of Oncology* 6:405-411, 1995, "Xiao") or alternatively, Skorski, *et al.* (*Blood* 86:726-736, 1995, "Skorski"). In particular, it is my understanding that the rejection is based on the following arguments.

4. Bonjouklian is characterized by the Examiner as describing administration of a phosphatidyl inositol 3 (PI3) kinase inhibitor, *e.g.*, wortmannin, to treat a PI3 kinase-dependent condition such as abnormal cell growth in a neoplasm such as ovarian cancer. Arnold is described in the rejection as teaching an increase in copy number of 3q26-qter in ovarian tumors. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention to detect amplification of the gene encoding the catalytic subunit of PI3 kinase, *i.e.*, *PIK3CA*, in ovarian cancer cells in a patient and to administer the PI3 kinase inhibitor wortmannin. Specifically, the Examiner contends that it would have been obvious because Arnold teaches that 3q26-qter is amplified in 42% of ovarian tumors that they analyzed and the *PIK3CA* gene is found at 3q26.3 (as taught by Volinia); and Bonjouklian teaches administration of a PI3 kinase inhibitor. The Examiner cites Xiao and Skorski as teaching that wortmannin inhibits proliferation of gastric cancer cell lines that overexpress PI3 kinase and of leukemia cells that require PI3 kinase for proliferation. It is the Examiner's position that Xiao and Skorski provide a basis for expecting that wortmannin treatment of ovarian cancer cells, as allegedly suggested by Bonjouklian, would inhibit proliferation.

5. This declaration is provided to show that the fact that the broad region of 3q26-qter was known to be amplified in ovarian cancer would not lead one of skill in the art to conclude that amplification of *PIK3CA*, which is one of numerous genes located in this broad region, leads to overexpression of *PIK3CA* and is therefore indicative of a role for PI3 kinase in oncogenesis in ovarian cancer cells that contain the amplified region.

6. Arnold describes a comparative genomic hybridization (CGH) study of forty nine ovarian cancer tumors. In this CGH analysis, differentially labelled total genomic DNA from a tumor sample and from a normal reference control sample were co-hybridized to normal metaphase chromosomes. The resulting ratio of the fluorescence intensities of the probes hybridized to the chromosomes is approximately proportional to the ratio of the copy numbers of the corresponding DNA sequences in the tumor and normal reference genomes. Arnold

identified the region of 3q26-qter as being increased in copy number in 42% of the ovarian tumors that were analyzed. However, although it was known in the art that the gene encoding the catalytic subunit of PI3 kinase (PIK3CA) is located at 3q26.3, the CGH study as performed by Arnold using metaphase chromosomes does not provide sufficient resolution to determine that the chromosomal subregion containing the PIK3CA locus is a focal point of amplification.

7. Furthermore, even though a gene may be present in an amplified chromosomal region, that fact alone does not lead one of skill to conclude that a particular gene is overexpressed. Many genes are present in chromosomal region 3q26-qter. For example the genome browser of the University of California, Santa Cruz (<http://genome.ucsc.edu/cgi-bin/hgTracks?hgSID=83748260&clade=vertebrate&org=Human&db=hg18&position=3q26&pix=620&Submit=submit&hgSID=83748260>), a print out of which is attached hereto, shows that numerous genes are located in the 3q26 region alone; however, there is no evidence that all or most of the products of these many genes are overexpressed in ovarian tumors.

8. It is my opinion as one who has practiced in this art for many years that although *PIK3CA* may have been identified as a potential gene of interest in the 3q26-qter region identified by Arnold due to its biological function in proliferation or its overexpression in other cancers, at the time of the invention one of skill could not have concluded that the mere presence of the gene in this broadly amplified region would predictably lead to a correlation with overexpression of the protein and an oncogenic role in ovarian cancer cell proliferation.

9. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon.

Dated: _____

Joe Gray, Ph.D.

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UCSC Genome Browser on Human Mar. 2006 Assembly

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chr3:	165000000	170000000	175000000	180000000	
	3q26.1	3q26.2	3q26.31	3q26.32	3q26.33
STS Markers					
BC033011	SI	WDR49 D	ARPM1	PLD1	NAALADL2
IFT80	SLITRK3	WDR49	MYNN	PLD1	NAALADL2
SMC4L1	BCHE	EVI1	TNIK	NLGN1	WIG1
SMC4L1	BCHE	EVI1	TNIK	ECT2	TBL1XR1
TRIM59	FLJ23049	MDS1	FNDCSB		PIK3CA
TRIM59	SERPINI2	MYNN	FNDCSB		KCNMB2
KPNR4	SERPINI2	MYNN	FNDCSB		FXR1
KPNR4	WDR49	SAND7	GHSR		WIG1
KPNR4	PDCD10	TLOC1	TNFSF10		FXR1
ARL14	SERPINI2	TLOC1	ARDACL1		SOX2
PPM1L	GOLPH4	PHC3	ECT2		
B3GALT3		LRRC34	FNDCSB		MFN1
B3GALT3	NMDS3	LRRC31	AF116526		MFN1
C3orf57		LRRC31	AK122096		GNB4
C3orf57		GPR160	ECT2		ACTL6A
		AK095225	ECT2		MRPL47
		PHC3	SPATA16		MRPL47
		PRKCI			MRPL47
		PRKCI			NDUFB5
		SKIL			NDUFB5
		SKIL			USP13
		CLDN11			PEX5L
		AK094547			PEX5L
		SLC7A14			PEX5L
		SLC7A14			TTC14
		BC107706			AT356762
		BCA49823			CCDC39
		EIF5A2			DNAJC19
		SLC2A2			
		SLC2A2			
		BC083582			
		AF316233			
		FNDCSB			
		FNDCSB			
RefSeq Genes					
BC101494	BC116452	BC105696	BC0858976	Mammalian Gene Collection Full	ORF mRNAs
BC113669	BC116453	BC069498	BC069498		BC017325
BC109259	BC115034	BC007269	BC026734		BC002696
BC109260	BC114621	BC033620	BC112086		BC0113601
BC028691	BC018141	BC032841	BC034496		BC0113603
BC034493	BC027859	BC0059386	BC032555		BC020506
BC125160	BC035512	BC022968			BC025161
BC125159	BC002506	BC107708			BC040557
BC034354	BC016353	BC036072			BC000873
BC104865	BC018043	BC060041			BC036371
BC104867		BC117401			BC001331
BC047618		BC117339			BC000949
BC028571		BC012035			BC032522
BC013317		BC000181			BC021575
BC065208		BC022016			BC0009796
BC107756		BC013577			BC005271
		BC033582			BC0093071
		BC0329297			BC016146
		BC069374			BC036163
		BC113547			BC028983
		BC032722			BC073989
		BC026228			BC009702
Human mRNAs					
Human ESTs That Have Been Spliced					
Spliced ESTs					
UniGene Alignments					
Hs.570534	Hs.542888	Hs.538450	Hs.533118	Hs.633891	Hs.614827
Hs.99333	Hs.581191	Hs.565856	Hs.609484	Hs.625103	Hs.581175
Hs.565665	Hs.565660	Hs.522045	Hs.589979	Hs.604354	Hs.573023
Hs.642893	Hs.408584	Hs.145428	Hs.561106	Hs.645764	Hs.587171
Hs.644252	Hs.126414	Hs.570532	Hs.439922	Hs.581635	Hs.607583
Hs.587174	Hs.638566	Hs.642130	Hs.629197	Hs.282012	Hs.573024
Hs.174743	Hs.533117	Hs.478143	Hs.31595	Hs.478289	Hs.613291
Hs.642432	Hs.542887	Hs.581631	Hs.599737	Hs.615069	Hs.435151
Hs.605563	Hs.254752	Hs.213762	Hs.570531	Hs.631074	Hs.31983
Hs.478895	Hs.361131	Hs.565855	Hs.614864	Hs.595126	Hs.644678
Hs.570686	Hs.586126	Hs.572920	Hs.389933	Hs.624265	Hs.645470
Hs.58992	Hs.572923	Hs.615832	Hs.619823	Hs.609436	Hs.596191
Hs.619330	Hs.615816	Hs.478153	Hs.542870	Hs.609781	Hs.542849
Hs.212957	Hs.581189	Hs.590095	Hs.33756	Hs.565848	Hs.570526
Hs.596326	Hs.542885	Hs.640896	Hs.164144	Hs.86024	Hs.645457
Hs.638605	Hs.574909	Hs.642534	Hs.603124	Hs.603646	Hs.563099
Hs.637607	Hs.528210	Hs.333400	Hs.167584	Hs.589975	Hs.542848
Hs.467866	Hs.642148	Hs.575028	Hs.598186	Hs.565849	Hs.581170
Hs.288193	Hs.429595	Hs.542877	Hs.46473	Hs.542857	Hs.635397
Hs.645996	Hs.627342	Hs.592880	Hs.34024	Hs.158830	Hs.642117
Hs.645655	Hs.627284	Hs.567961	Hs.362855	Hs.416922	Hs.625296
					Hs.581646

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Map ContigsAssemblyGapCoverageBAC End PairsFosmid End PairsGC PercentShort MatchRestr Enzymes**Phenotype and Disease Associations**Locus Variants**Genes and Gene Prediction Tracks**Known Genes

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Ensembl GenesAceView GenesN-SCANSGP GenesGeneid GenesExoniphySuperfamilyEvoFoldsno/miRNA**mRNA and EST Tracks**Human mRNAs

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Spliced ESTs

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Human ESTsOther mRNAsOther ESTsH-InvUniGene

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Poly(A)**Expression and Regulation**Affy HuEx 1.0Allen BrainGNF Atlas 2GNF RatioBertone Yale TARAffy U133Affy GNF1HAffy U133Plus2Affy U95FirstEFTFBS ConservedORegAnno7X Reg Potential**Comparative Genomics**Conservation

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Most ConservedFugu ChainFugu NetTetraodon ChainTetraodon NetTetraodon EcoresZebrafish chainZebrafish NetX. tropicalis ChainX. tropicalis NetChicken ChainChicken NetOpossum ChainOpossum NetCow ChainCow NetDog ChainDog NetRat Chain

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